Neurobiological and Clinical Consequences of Stress

From Normal Adaptation to Post-Traumatic Stress Disorder

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18

Clinical Studies of Neurotransmitter Alterations in Post-Traumatic Stress Disorder

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Many of the earliest terms for post-traumatic stress disorder (PTSD), such as "shell shock" (1), reflected the belief that post-traumatic clinical symptomatology was linked to an underlying disturbance of the nervous system. Some believed that the physical shock from exploding shells actually caused permanent alterations in brain structure, leaving the shell-shocked veteran in a chronic state of hypersensitivity and hyperarousal. To distinguish this condition from other neuroses and to emphasize its physiological underpinnings, Kardiner coined the term "physioneurosis" in 1941 (2). In addition to hypervigilance, insomnia, irritability, and hyperarousal, veterans with shell shock or physioneurosis suffered from symptoms of "reexperiencing" and "avoidance."

Although preliminary neurobiologic investigations of combat trauma began as early as 1918, most biologic studies of trauma have been conducted since 1980 when PTSD was added to the formal nosology of the DSM-III. As a result, unlike preclinical stress data, the number of neurobiologic investigations directly related to human trauma is relatively small. Nevertheless, over the past decade, a series of psychophysiologic, hormonal, neurotransmitter, receptor binding, electrophysiologic and brain imaging studies have begun to characterize the biological nature of this disorder.

In this chapter we will describe and summarize clinical studies of neurotransmitter alterations in PTSD. While preclinical studies of stress have repeatedly demonstrated alterations in multiple neurotransmitter systems, studies in traumatized humans have largely been limited to the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis studies are summarized in Chapter 19. In this chapter we will focus primarily on sympathetic nervous system neurotransmitters (norepinephrine, epinephrine, and dopamine), although mention will be made of opiate and serotonin systems.

It is important to note that other neurotransmitter systems are also likely involved in the fight-flight response. Furthermore, because neurotransmitter systems are closely interrelated, it is difficult, if not impossible, to determine accurately the specific behavioral effects of a single neurotransmitter. For example, the HPA axis and sympathetic nervous system appear to modulate one another during acute stress (3).

In humans, most biological studies of PTSD have involved combat veterans. As a result, much of what is discussed in this chapter draws heavily on findings from this patient population. It is important to note, however, that PTSD can develop in response to a wide variety of traumatic stressors, including natural disasters, vio-

lent crimes, accidents, child abuse, and war. To the extent that neurobiologic alterations are related to the core symptoms of PTSD, it would be anticipated that findings from combat veterans will be replicated in civilian populations, since the core symptoms of PTSD are similar across all traumas.

Although to date numerous techniques and strategies have been used to study neuroendocrine alterations in PTSD, it is useful to classify these studies into two major categories: 1) naturalistic or baseline observations (Table 1), and 2) challenge strategies (Table 2). In naturalistic studies, components of a particular neurobiologic system are investigated under normal resting conditions. The goal of these studies is to examine the biological systems of interest as they function under normative conditions, without external provocation. Clearly, however, the process of informing an individual that he or she is being evaluated, reviewing potential hazards of the study, obtaining informed consent, attaching electrodes, drawing blood, etc., may serve as environmental influences that impact on the study measures. Challenge strategies, on the other hand, are designed to evaluate biological systems under controlled conditions that intentionally provoke the system. Behavioral, physiologic, and neuroendocrine responses are typically measured after provocation with external stimuli such as trauma scripts or exogenously administered biological substances. When baseline and challenge strategies are used in tandem, it is possible to obtain more complete information about the nature and origin of biological alterations.

SYMPATHETIC NERVOUS SYSTEM

In order to maximize both mobilization and utilization of energy under conditions of extreme stress, the sympathetic nervous system tends to discharge as a unit. Coordinated sympathetic discharge will: 1) shunt blood from temporarily unnecessary splanchnic and renal regions to active muscle groups; 2) rapidly increase energy supply to skeletal musculature by mobilizing blood glucose; 3) accelerate heart rate and increase blood pressure, allowing for greater perfusion of muscles and vital organs; 4) dilate pupils so that more light enters the eye; and 5) constrict skin vasculature in order to limit blood loss should injury occur (4,5). Widespread emergency-stimulated sympathetic nervous system discharge prepares the organism for what Cannon termed the "flight or fight" response (6).

While stress-induced sympathetic nervous system activation serves a protective role in the short run, it appears that long-term negative sequelae may ensue for some individuals. That is, the sympathetic nervous system appears to become hyperresponsive to a host of trauma-related stimuli in many individuals who develop PTSD. The nature and extent of this hyperresponsiveness have been the subject of intense recent study and now will be summarized.

HISTORICAL FRAMEWORK FOR STUDIES OF NERVOUS SYSTEM ALTERATIONS IN PTSD

In 1918, two studies became the first laboratory investigations of sympathetic nervous system activity among traumatized humans. First, Meakins and Wilson exposed combat veterans with shell shock to sounds of gunfire and the smell of sulfuric flames, and found that as a group they had greater increases in heart rate and respiratory rate than healthy controls (1). Second, Fraser and Wilson demonstrated exaggerated psychophysiologic arousal with marked increases in subjective anxiety, heart rate, and blood pressure among war veterans compared to healthy controls in response to intravenous epinephrine (EPI) administration (7).

During World War II, Grinker and Spiegal described combat soldiers who appeared to suffer from a chronic stimulation of the sympathetic nervous system. "They perspire freely, are tremulous, restless, irritable, sleep poorly, and look very sick. At times these symptoms suddenly increase, especially in response to mild auditory and verbal stimuli, and the patients react as if they have received an injection of adrenalin" (8). This belief that altered catecholamine function played a critical role in combat neurosis led some clinicians and researchers to advocate

bilateral denervation of the adrenal glands as a form of treatment for highly symptomatic war veterans (9).

The first contemporary psychophysiological study in combat veterans was performed by Dobbs and Wilson (10), who demonstrated that combat sounds led "decompensated" World War II soldiers to become more agitated compared with World War II soldiers who were not described as decompensated. Since 1980, there has been a series of psychophysiology studies measuring heart rate, blood pressure, and galvanic skin response at baseline and in response to trauma-related cues (11–20). The data have shown marked elevations in psychophysiologic parameters during provocation but few, if any, differences at baseline between combat veterans and normal controls. This hyperreactiveness has not been observed in combat veterans without PTSD (16) or in combat veterans with anxiety disorders other than PTSD (21), suggesting that neither combat alone nor the presence of anxiety disorders other than PTSD is sufficient to explain postwar physiologic reactivity. Furthermore, hyperreactive psychophysiologic responses to reminders of trauma also have been observed in civilians with PTSD. For example, Blanchard et al., while studying victims of motor vehicle accidents, found heart rate, systolic blood pressure, and electrodermal activity to be significantly elevated in response to personal trauma-related cues among subjects who developed PTSD compared to those who did not develop PTSD (22). Similarly, Shalev et al. reported significant responses to traumatic imagery in Israeli civilians with post-traumatic stress disorder (20).

Indeed, consistent alterations in psychophysiologic responses to stress-related stimuli in humans prompted researchers to investigate the biochemical underpinnings of sympathetic nervous system activation in traumatized populations. These studies have primarily focused on norepinephrine (NE), EPI, and dopamine (DA), the three key sympathetic nervous system neurotransmitters.

CATECHOLAMINE ALTERATIONS IN PTSD

An enormous body of preclinical literature has been devoted to the relationship between stress and catecholamines. For example, it has been shown repetitively that stressful or fearful stimuli of many types produce marked increases in central and peripheral NE. Noradrenergic

TABLE 1. *Baseline catecholamine studies in PTSD*

	Compared to controls	References
24-hour urine		
Norepinephrine	Increased	Kosten et al. (31), Yehuda et al. (30) Davidson and Baum (33)[a]
	No difference	Pitman and Orr (32)[b]
Epinephrine	Increased	Kosten et al. (31), Yehuda et al. (30)
	No difference	Pitman et al. (32)[b]
Dopamine	Increased	Yehuda et al. (30)
Plasma		
Norepinephrine	No difference	McFall et al. (34), Blanchard et al. (13) Hamner et al. (35), Southwick et al. (36)
Epinephrine	No difference	McFall et al. (34)
MAO activity	Decreased	Davidson and Baum (33)
Receptors		
$Alpha_2$ receptors	Decreased	Perry et al. (40)
cAMP	Decreased	Lerer et al. (48,49) 1987, 1990

[a]Eight-hour urine collection
[b]Compared to combat controls
MAO, monoamine oxidase; PTSD, post-traumatic stress disorder.

TABLE 2. *Catecholamine challenge studies in PTSD*

	Compared to controls	Reference
In Vitro Studies		
Epinephrine/alpha$_2$ receptors	Increased responsivity	Perry et al. (39)
Isoproterenol/cAMP	Decreased responsivity	Lerer et al. (48)
Forskolin/cAMP	Decreased responsivity	Lerer et al. (48) (49)
Non Trauma-related Stressors		
Exercise stress/NE	Increased responsivity	Hamner et al. (35)
Noncombat film/NE	No difference	McFall et al. (34)
Simulated Traumatic Stressor		
Combat film/E	Increased responsivity	McFall et al. (34)
Combat sounds/NE	Increased responsivity	Blanchard et al. (13)
Neuroendocrine Challenge		
Desipramine/growth hormone	No difference	Dinan et al. (60)
Clonidine/growth hormone	Decreased responsivity	Hansenne et al. (61)
Lactate	Increased responsivity	Rainey et al. (63)
Yohimbine/MHPG	Increased responsivity	Southwick et al. (36)
Yohimbine/Startle	Increased responsivity	Morgan et al. (57)
Yohimbine/Cerebral metabolism	Decreased metabolism	Bremner et al. (69)

brain systems appear to play a critical role in orientation to novel stimuli, vigilance, selective attention, and cardiovascular responses to life-threatening situations (23). Although acute stress-related elevations of NE appear to serve a protective role for the organism, accumulating evidence suggests that certain types of stress, especially uncontrollable stress, can contribute to chronic maladaptive alterations in catecholaminergic systems (24). Thus, for example, preclinical investigations have shown that uncontrollable stress can cause chronic increased responsivity of locus coeruleus neurons to excitatory stimulation (25,26), as well as an associated subsensitivity of alpha-2-adrenergic receptors and a decreased number of postsynaptic beta-adrenergic receptors (27,28). (For a review of stress and catecholamines, see Murburg (29) and Chapter 9 of this volume.)

Baseline Studies (Table 1) NE Studies

Mean 24-hour urinary excretion of NE has been found to be elevated in combat veteran inpatients with PTSD compared to normal controls (30), and compared to psychiatric patients with major depression and schizophrenia (31). In combat veterans with PTSD, Kosten and colleagues reported a mean NE level of 76±10 μg/day (31) while Yehuda et al. (30) and Pitman and Orr (32) reported mean NE levels of 56±14 μg/day and 60.8±26.1 μg/day respectively. Pitman and Orr (32) additionally reported that combat veterans without PTSD had a mean NE level of 58.0±35.0 μg/day, which was not statistically different from combat veterans with PTSD. In contrast, the mean NE levels reported for normals has been 32±10 μg/day (30). Although Pitman and Orr concluded that similar NE values for combat veterans with and without PTSD indicated a failure to replicate the Kosten et al. (31) study, their findings may indicate that combat veterans without PTSD, like combat veterans with PTSD, exhibit an elevation of 24-hour urinary catecholamines. Thus, alterations in NE excretion may be a function of trauma, rather than the disorder of PTSD per se. Further studies using all three groups (i.e., combat veterans with PTSD, combat veterans without PTSD, and nontraumatized individuals without psychiatric disorder) are necessary to clarify this issue.

In a study of civilians, Davidson and Baum (33) measured urinary catecholamine levels in a community sample of individuals living within 5 miles of the Three Mile Island nuclear power station 5 years after the accident. The authors found higher urinary NE levels in residents living closer to Three Mile Island compared those living 80 miles away. These results implied in-

creased "stress" levels in individuals with greater exposure to the accident based on proximity. However, Davidson and Baum did not assess subjects for the presence or absence of PTSD.

Unlike findings from 24-hour urine studies, baseline plasma NE investigations have generally reported no significant differences between PTSD patients and normal controls (13,34). McFall et al. (34) and Blanchard et al. (13) in separate studies measuring NE response to war-related laboratory stimuli both reported resting NE values that were similar in PTSD patients and controls. Hamner et al. (35) similarly found no baseline differences between PTSD patients and controls. As part of a yohimbine infusion study, Southwick et al. (36) reported comparable baseline plasma levels of the major norepinephrine metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), in PTSD patients and controls. It should be noted, however, that these studies typically use NE values obtained by single-stick venipuncture, which may not provide an accurate baseline catecholamine measure due to the stress of the venipuncture itself (37).

EPI and DA Studies

Twenty-four-hour urinary DA and EPI excretion also have been reported as elevated in combat veterans with PTSD (30,31). The urinary DA finding is consistent with Hamner et al.'s report of significant elevations in plasma DA among 12 Vietnam combat veterans with PTSD compared with major depressed patients and healthy controls (38). Studies of urinary EPI, on the other hand, have been less consistent. While Kosten et al. (31) and Yehuda et al. (30) both reported increased levels of 24-hour urinary EPI excretion among inpatients with PTSD, Pitman and Orr (32) did not find an elevation. In a study measuring baseline plasma EPI in PTSD and non-PTSD subjects, McFall et al. (34) found no differences between groups. Finally, in the just mentioned Yehuda et al. study (30), urinary NE and DA, but not EPI excretion, correlated with severity of PTSD symptomatology, particularly intrusive symptoms.

Adrenergic Receptor Function

Alpha-2-adrenergic receptors play an important role in translating the neurochemical message of NE and EPI, and as such may provide information about the longterm effects of alterations in catecholamine neurotransmission. It has further been suggested that alpha-2-adrenergic receptor activity may reflect overall sympathetic "tone" (39). Perry et al., in two separate radioligand bindings studies—one involving combat veterans (40) and the other investigating traumatized children (41)—found fewer total alpha-2-adrenergic receptor binding sites per platelet in subjects with PTSD compared to controls. Similar findings have been noted in medical illnesses characterized by excessive catecholamine hypersecretion, such as congestive heart failure (42) and hypertension (43). Interestingly, decreased alpha-2 adrenergic receptor number also has been demonstrated in patients with borderline personality disorder (44,45). It is possible that borderline personality disorder and PTSD share a common neurobiologic alteration of the noradrenergic system. Indeed, it has been recently demonstrated that treatment-seeking combat veterans with PTSD show an unusually high incidence of borderline personality disorder (46). As discussed by Perry, chronic elevation of circulating catecholamines may explain this decrease in receptor number (39). Of note, in a separate study, comparison groups of patients with major depression and generalized anxiety disorder both had significantly greater numbers of platelet alpha-2-adrenergic receptors than PTSD patients, suggesting that PTSD differs from these two disorders with regard to regulation of catecholamine metabolism (47).

Finally, Lerer et al. examined adenylate cyclase activation in platelet membranes, as well as adenosine 3',5'-cyclic phosphate (cAMP) signal tranduction in both platelet membranes and intact lymphocytes of PTSD patients. In separate studies, basal cAMP (48) and basal adenylate

cyclase (49) levels were noted to be lower in PTSD patients compared to controls.

Challenge Studies (Table 2)

To date, four different challenge strategies have been applied to the study of the neurobiology of PTSD. These include in vitro paradigms, provocation with nontrauma-related stressors, provocation with trauma-related stressors, and neuroendocrine challenges. Each of these strategies will now be described.

In Vitro Paradigms

An in vitro challenge refers to an experimental paradigm in which the biological system of interest, (e.g., a platelet preparation containing alpha-2 receptors) is isolated from the organism, maintained in a "live" state, and then subjected to exogenous stimulation. Such a paradigm allows investigators to directly control a host of variables that would be difficult if not impossible to account for in the living organism. To investigate dynamic functioning and regulation of the alpha-2-adrenergic receptor in patients with PTSD, Perry exposed intact platelets to high concentrations of EPI. Typically, in response to agonist binding (as is the case with EPI), a percentage of receptor recognition proteins are physically taken into the cell in a process called internalization. While internalized, the receptor site is no longer available for radioligand binding. Compared to controls, EPI-incubated platelets of PTSD patients showed a more rapid and extensive loss of receptor protein from the platelet membranes. These findings appear consistent with a receptor-effector system that has been overtaxed and is now easily "fatigued" and more sensitive to downregulation (39).

A second series of in vitro investigations has involved forskolin stimulation of lymphocyte and platelet preparations, as well as isoproterenal stimulation of lymphocyte preparations. In lymphocyte preparations, lower responsiveness to isoproterenol and forskolin stimulation was noted in PTSD patients compared to controls (48,49). Similarly, in platelet membrane preparations the patient group was found to have lower responsiveness to forskolin stimulation. These findings appear to reflect a diminished responsivity of the receptor adenylate-cyclase complex in patients with PTSD. Together with Perry et al.'s finding (39–41), these reports point to potential abnormalities at both the adrenergic receptor level and at sites distal to the receptor.

Provocation with Nontrauma Related Stressors

In PTSD, very few reports have examined relative differences between individuals with PTSD and individuals without PTSD in basic stress parameters. Therefore, to date, information concerning the basic stress response is limited. In one study using an exercise treadmill, Hamner et al. (35) investigated the effects of physical stress on plasma catecholamines in 12 combat veterans with PTSD and in 8 normal controls. The two groups did not differ significantly in maximal blood pressure and heart rate response to exercise, pre- and post-test NE levels, or percent increase in mean plasma norepinephrine. However, plasma MHPG levels increased significantly in the PTSD patients but not in the controls. The authors note that an exaggerated MHPG response suggests increased sensitivity to noradrenergic activation in the PTSD group after exposure to a physical stressor unrelated to combat trauma. In contrast to these findings, McFall et al. (34) measured psychophysiological reactivity, circulating plasma catecholamines, and subjective distress in 10 combat veterans with PTSD and 11 controls in response to a film depicting an automobile accident. Although combat veterans with PTSD reported greater subjective distress, they did not show any differences compared to normals on any measure of autonomic arousal, including heart rate, blood pressure, NE, and EPI. It should be stated that the sample size in both of these studies is probably too small to allow sufficient power for detecting differences. Therefore, negative results may be attributed to an insufficient subject number, whereas a positive result in such studies may be the result of chance. Clearly, further

studies are needed to clarify these interesting questions.

Another line of neurobiological investigation with potential relevance to neurotransmitter alterations in PTSD involves the acoustic startle response. Startle is a ubiquitous cross species, mammalian CNS response to a sudden exteroceptive stimulus (50). The organism may startle in response to visual, tactile, and auditory stimuli. The startle response is measured as a whole-body movement in the rat and as the magnitude of the eyeblink response in humans. Because startle is a brainstem-mediated response, it may afford a means more direct than cardiac reactivity for investigating the CNS in individuals who have been traumatized. When the organism is presented with a stimulus that is conditioned to fear, startle increases (51). Study of the startle reflex, especially fear-potentiated startle, may have relevance to PTSD since accentuated startle is a cardinal symptom of PTSD in humans, and since preclinical studies have shown that magnitude of startle is sensitive to manipulations of several neurotransmitter systems hypothesized to be involved in the pathophysiology of PTSD (52). For example, drugs that increase NE transmission and that have been associated with increased fear also increase fear-potentiated startle. Thus, in the rat, NE and fear-potentiated startle both increase after yohimbine administration and decrease after infusion of clonidine (53). To date, studies in traumatized humans have largely shown normal acoustic startle in the absence of stressful test conditions (54–56). However, recent data suggest that startle may be more pronounced in subjects with PTSD than in controls under conditions of fear and during hyperadrenergic states (57–59).

Provocations with Trauma-related Stressors

In addition to the psychophysiological studies just reviewed and those summarized in Chapter 16, a number of investigations have measured stress-induced psychophysiologic and catecholamine responses in parallel. McFall et al. (34) found higher levels and a parallel rise in subjective distress, blood pressure, heart rate, and plasma EPI during and after a combat film among combat veterans with PTSD compared to controls. This parallel rise suggested that heightened physiological reactivity was indeed related to circulating catecholamines, more specifically to EPI. Because the increase in EPI and other indices of sympathetic nervous system activity were more pronounced in response to combat-related stimuli than noncombat related stimuli, the authors interpreted these findings as being consistent with the idea that biological responses may be conditioned in PTSD. In a similarly designed study involving combat veterans with and without PTSD, Blanchard et al. measured plasma NE and heart rate before and after exposure to auditory stimuli reminiscent of combat. Veterans with PTSD had significantly greater increases in both NE and heart rate than controls (13).

Neuroendocrine Challenge Studies

The desipramine growth hormone challenge has been used as a probe of postsynaptic alpha-2-adrenergic receptor function in a study of eight traumatized women. Dinan et al. found no difference between traumatized subjects and controls in desipramine-stimulated growth hormone levels (60). Hansenne et al. reported a blunted growth hormone response to intravenous clonidine in a 20-year-old car accident victim with PTSD (61). Since the growth hormone response to clonidine is generally thought to be an index of noradrenergic function, blunting suggested heightened noradrenergic sensitivity with possible downregulation of noradrenergic receptors. After successful treatment, the authors reported a normal growth hormone response to clonidine that they interpreted as further evidence for a relationship between noradrenergic dysregulation and PTSD-specific symptoms (61).

Intravenous lactate infusion has been shown to cause panic attacks in patients with panic disorder (62). Although the precise mechanism of lactate-induced anxiety and panic is not known, central noradrenergic stimulation has been suggested. In a study of seven Vietnam veterans with PTSD, Rainey et al. reported panic

attacks in six of seven subjects and flashbacks in all seven (63). However, because the six subjects who had lactate-induced panic attacks also met criteria for comorbid panic disorder, it was not possible to determine whether the responses were secondary to panic disorder, PTSD, or both.

Yohimbine, a more direct probe of noradrenergic activity, has been tested in 20 Vietnam combat veterans with PTSD compared to 18 controls. Yohimbine is an alpha-2-adrenergic receptor antagonist that activates noradrenergic neurons by blocking the alpha-2-autoreceptor, thereby increasing presynaptic noradrenergic activity. Although yohimbine acts on multiple neurotransmitter systems, at the dose employed in this study, its primary effect is on the noradrenergic system (64). Yohimbine produced panic attacks in 70% and flashbacks in 40% of patients with PTSD (36). There were no yohimbine-induced panic attacks or flashbacks among the control group. A more than twofold greater elevation of plasma MHPG following yohimbine administration suggested abnormal presynaptic noradrenergic reactivity in the PTSD patients.

With regard to specificity, yohimbine has not produced similar effects in MDD, schizophrenia, obsessive-compulsive disorder, or even generalized anxiety disorder (65). However, it has resulted in comparable behavioral and cardiovascular responses in panic disordered patients (66), suggesting that PTSD and panic disorder share a common neurobiological abnormality related to altered sensitivity of the noradrenergic system. Importantly, because 43% of the patients with PTSD who had yohimbine-induced panic attacks in this study did not meet comorbid criteria for panic disorder, the yohimbine-induced panic attacks could not be explained solely by the presence of panic disorder. On the other hand, patients meeting criteria for both panic disorder and PTSD had an 89% incidence of yohimbine-induced panic attacks. It may be that comorbid panic disorder in patients with PTSD simply reflects a more pronounced abnormality of the noradrenergic system. This notion is supported by recent evidence suggesting that comorbid panic disorder in some patients with PTSD is most likely trauma-induced rather than familial in origin (67).

In both normal subjects and in combat veterans with PTSD, yohimbine also has been used as a biological probe to study the effects of catecholamine transmission on the acoustic startle reflex (57,68). As predicted by preclinical studies, Morgan et al. found that yohimbine significantly increased both startle reflex and serum MHPG in normal subjects (68). These increases were significantly correlated in time, suggesting that magnitude of startle was related to catecholamine transmission. In a separate study, yohimbine infusion caused significantly greater increases in acoustic startle among PTSD patients compared to controls (57). Although MHPG from this study has not yet been analyzed, in prior published work yohimbine has been shown to produce greater increases in MHPG among combat veterans with PTSD compared to normal subjects (36). Taken together, these studies suggest that exaggerated startle in patients with PTSD may indeed be related to increased noradrenergic transmission. Of note, however, because preclinical data has clearly implicated other neurotransmitters in exaggerated startle, it is likely that exaggerated startle seen in humans with PTSD is modulated by multiple transmitters.

To study the effects of yohimbine on brain metabolism, a single bolus of [F-18]2-fluoro-2-deoxyglucose (FDG) was administered to 10 Vietnam combat veterans with PTSD and 10 healthy age-matched controls immediately following either yohimbine or placebo infusion. Subjects were then scanned for 60 minutes, and a PET image was reconstructed at 30–50 minutes postinjection in order to determine brain tissue activity (69). Consistent with this reported yohimbine study, 6 of 10 PTSD patients had a panic attack and 3 of 10 a flashback in response to i.v. yohimbine but not placebo. A significantly different metabolic response to yohimbine in neocortical brain regions (prefrontal, temporal parietal, orbitofrontal cortices) was noted in patients compared to controls, with controls showing a tendency toward increased and PTSD patients a tendency toward decreased metabolism.

The authors note that these findings agree with preclinical data that supports a dose response effect of NE on brain metabolism where lower levels of NE result in increased metabolism and higher levels in decreased metabolism. Thus, it is hypothesized that PTSD patients, being unusually sensitive to yohimbine, release more NE in response to yohimbine, with a resultant decrease in brain metabolism. This decrease in brain metabolism may cause an increase in signal-to-noise ratio of neuronal activity, with an increase in selective attention or neuronal responsivity to relevant stimuli and a decrease or suppression of background neuronal activity. It is possible that chronic hyperarousal and hypervigilance in individuals with PTSD are related to the effects of increased responsivity of brain catecholamine systems.

SEROTONERGIC ALTERATIONS IN PTSD

Although only two studies have directly examined the 5-HT system in PTSD, a large body of indirect evidence suggests that this neurotransmitter may be important in the pathophysiology of trauma-related symptomatology. In humans, low serotonin (5-HT) functioning has been associated with aggression (70), impulsivity (70), and suicidal behavior (71). Patients with PTSD are frequently described as aggressive or impulsive, and often suffer from depression and suicidal tendencies. Further evidence comes from the observation that serotonin reuptake inhibitors have been found to be partially effective in treating PTSD symptoms such as intrusive memories and avoidance symptoms (72–75).

Baseline Studies

The first report of serotonergic function in PTSD was a study examining paroxetine binding in blood platelets of 20 combat veterans with PTSD under baseline conditions (76). In this study, platelet 5-HT uptake was significantly decreased in PTSD patients compared with normals, and in PTSD patients meeting criteria for comorbid major depressive disorder. Because decreased platelet 5-HT uptake also has been reported in patients with depression and alcoholism, the specificity of these findings has yet to be determined.

Provocation Studies

More recently, the behavioral effects of m-chloro-phenyl-piperazine (MCPP) have been examined in a preliminary study of 14 combat veterans with PTSD (77). MCPP is a 5-HT agonist with predominant effects on 5-HT2 and 5-HT1c receptors. Five of the 14 patients with PTSD had a panic attack and 4 had a flashback following MCPP administration. In contrast, no patient had a panic attack and one patient experienced a flashback following infusion of placebo saline. Thus, a subgroup of patients with PTSD exhibited a marked behavioral sensitivity to serotonergic provocation, raising the possibility of pathophysiologic subtypes among traumatized combat veterans.

Clearly, further studies are needed to delineate possible serotonergic alterations in PTSD. For example, in mood and anxiety disorders, baseline studies of serotonergic function have included measures such as cerebrospinal concentrations of 5-hydroxyindolcacetic acid and platelet 3H-imipramine binding as well as estimates of 5-HT and 5-HIAA content in blood and urine. More recently, a variety of challenge strategies has been used to study the function and sensitivity of the 5-HT system in psychiatric disorders. In addition to MCPP, investigators have studied behavioral and neuroendocrine responses to fenfluramine, tryptophan infusion, and tryptophan depletion. Future studies using these paradigms would help to clarify the possible role of serotonergic systems in PTSD.

OPIATES

Stress causes a release of endogenous opiates, increased opiate peptide levels, and diminished pain sensitivity (78–80). The fact that stress-induced analgesia can be blocked by administra-

tion of an opiate antagonist, naltrexone hydrochloride, supports the notion that stress, endogenous opiates, and analgesia are related (80–82). Additionally, evidence suggests that analgesia can accompany neutral stimuli previously paired with aversive stimuli (83). Furthermore, it appears that the endogenous opiate system can become sensitized so that reexposure to lower levels of uncontrollable shock results in the same degree of analgesia previously induced by significantly greater degrees of shock (82). Given these facts, it is reasonable to study opiate systems in individuals who have been severely traumatized.

Baseline Studies

Only two laboratory reports have described baseline opiate metabolism in traumatized humans. Hoffman et al. (84) reported significantly lower a.m. and p.m. plasma b-endorphin levels in 21 PTSD patients compared to 20 controls. The results were viewed as support for van der Kolk's hypothesis (85) that patients with PTSD have a chronic depletion of endogenous opioids and that hyperresponsiveness is related to endogenous opiate withdrawal. According to this hypothesis, patients with PTSD seek out or provoke recurrent stressors and traumas in order to increase opiate release, and hence decrease endogenous opiate withdrawal.

The second baseline study (86) measured circulating levels of methionine-enkephalin and its in vitro plasma degradation half-life in 13 Vietnam combat veterans with PTSD compared to controls. While plasma methionine-enkephalin levels were similar in PTSD patients and controls, degradation half-life was significantly higher in the PTSD group. The authors suggest the possible existence of a circulating endogenous inhibitor of methionine-enkephalon degradation. However, such a substance has never been isolated. The authors further speculate that decreased degradation in the face of normal plasma methionine-enkephalin levels may suggest decreased production and release of this peptide. Although it is suggested that these findings are consistent with those of Pitman et al. (80) (summarized in the next section), it is more likely that the findings are compatible with the notion of a chronic baseline opiate depletion. Because the Hoffman et al. and Wolfe et al. studies measured different opiates, a direct comparison of the results is not feasible.

Provocation Studies

To date, only one challenge study has focused on the opiate system in PTSD. Pitman et al. (80) exposed eight combat veterans with PTSD and eight combat controls to the stress of a combat film. Following the film, subjects were exposed to a pain sensitivity test. Veterans with PTSD showed reduced pain sensitivity compared to veterans without PTSD. This effect was reversible with the opiate antagonist nalaxone. These findings suggest that stress-induced analgesia is, at least in part, mediated by endogenous opiates and that patients with PTSD show an enhanced release of endogenous opiates following exposure to stress. The results of the Pitman et al. study differ from the results of baseline studies. In baseline studies, it appears that opiate levels are either normal or reduced. However, the Pitman et al. study suggests enhanced opiate release in response to a stressful stimulus. The Pitman et al. study fails to support van der Kolk's hypothesis of a biologically-mediated "addiction to trauma" in PTSD, as combat films in veterans with PTSD evoked numbing and blunting of emotional responses as opposed to euphoria or emotional feelings of calm and control. Studies of self-mutilation in traumatized psychiatric patients further support a relationship between psychic numbing and opiate-mediated, stress-induced analgesia (87).

Whether alterations in endogenous opiates contribute to the core symptoms seen in PTSD is not clear. However, based on the studies just discussed, it has been hypothesized that symptoms of avoidance and numbing are related to a dysregulation of opioid systems in PTSD (88). Furthermore, it has been suggested that the use of opiates in chronic PTSD may represent a form of self-medication (88,89). Animal studies have shown that opiates are powerful suppressants

of central and peripheral noradrenergic activity (90). If, as suggested earlier in this chapter, some PTSD symptoms are mediated by noradrenergic hyperactivity, then opiates may serve to "treat" or dampen that hypersensitivity and the accompanying symptoms. On the other hand, during opiate withdrawal when opiates are decreased and noradrenergic activity increased, PTSD symptoms may become acutely exacerbated. In fact, many symptoms of PTSD have been compared to symptoms experienced during opiate withdrawal (91).

SUMMARY AND CONCLUSION

In summary, baseline or resting studies generally have found no differences in plasma catecholamine levels between combat veterans with PTSD and normal controls. In contrast, most 24-hour urine studies have reported increased excretion of catecholamines and most challenge studies have found evidence for hyperresponsivity of catecholaminergic systems. It is possible that the discrepancy between single plasma samples versus 24-hour urine values is explained by phasic increases in catecholamine reactivity that are detected and accounted for through the use of 24-hour but not single plasma samples. That is, catecholamine levels in 24-hour urine samples reflect the summation of both phasic physiologic changes in response to meaningful stimuli (as seen in challenge studies) and tonic resting levels of catecholamines, while single plasma samples reflect only tonic activity.

In the aggregate, the aforementioned investigations point to an increased responsivity of the sympathetic nervous system detectable under conditions of "stress" in severely traumatized individuals with PTSD. These findings are consistent with a large body of psychophysiologic data recently reviewed by Orr (92) that shows consistent increases in psychophysiologic reactivity to trauma-related cues in combat veterans with PTSD. Consistent psychophysiologic evidence of resting or baseline elevations has not been found across studies (92). Because far less is known about the serotonin and opiate systems in PTSD, no real conclusions can be drawn except that alterations in these systems also appear to be most easily detected under conditions of "stress" or provocation.

The findings just discussed are consistent with a behavioral sensitization model of PTSD. Behavioral sensitization refers to an increased magnitude of response following repeated presentations of a particular stimulus. Following a stressful event, biochemical, physiologic, and behavioral responses to subsequent stressors increase over time. For example, when animals are exposed to repeated shock, dopamine beta-hydroxylase activity, tyrosine hydroxylase, and synaptic levels of NE all increase (93–95). When exposed to a limited shock, these repeatedly shocked animals respond as if the shock were much greater and release an amount of NE that is appropriate for a much larger stressor. Thus, a compensatory increase in NE synthesis and subsequent release appears to occur over time.

There are a number of parallels between PTSD and laboratory-induced behavioral sensitization. First, prior exposure to traumatic stressors can increase subsequent responses to stressors, depending on initial dose of exposure as well as frequency and intermittency of exposure (96–98). For example, animals that receive a large initial dose of cocaine show greater behavioral responses on reexposure than animals that receive a low dose of cocaine initially (99). Similarly, in traumatized humans severity of PTSD symptomatology is positively correlated with magnitude of traumatic exposure (100,101) and prior exposure to childhood trauma (102). In a study of Israeli combat soldiers who fought in two successive wars, Soloman et al. reported that soldiers were more likely to develop symptoms during the second war if they had suffered acute combat stress during the first one (103).

Second, for many patients with PTSD, symptoms increase in magnitude over time. In a study of WWII veterans 20 years after the war, Archibald and Tuddenham reported an increase in symptoms among patients with PTSD over time (104). In a retrospective study of treatment-seeking Vietnam combat veterans with PTSD, Bremner et al. found that symptomatology typically increased over the first few years after the war

and then plateaued, becoming chronic and unremitting (105). Similarly, animal studies of behavioral sensitization, and what Antelman has termed "time dependent change" (106) have shown that stressors can cause longlasting and gradually increasing changes in behavioral and physiological responses to subsequent stressors.

Increased sensitivity and sensitization of the noradrenergic system, as detected by the provocation studies mentioned in the previous paragraph, may leave the individual in a hyperaroused, vigilant, sleep-deprived, and, at times, explosive state that worsens over time. Being irritable and on edge makes it difficult to interact with family members, friends, coworkers, and employers. To quiet these symptoms of hyperarousal, PTSD patients often withdraw and become avoidant. Many also resort to substances, particularly central nervous system depressants, that suppress peripheral and central catecholamine activity. Alterations in other neurobiologic systems may further contribute to multiple symptoms such as intrusive memories, dissociative phenomena, and even numbing. Clearly, prospective biological studies in recently traumatized humans are needed to better assess behavioral sensitization as a model for the natural evolution of PTSD-related symptomatology.

Other models that may be relevant to aspects of PTSD include fear conditioning (51–53), overconsolidation of memory (17,107,108), and failure of extinction (88). Although these models have been offered as paradigms of the neurobiology of PTSD, there is not yet enough empirical neurobiologic data in humans to adequately support any one model. Nonetheless, these models may serve as useful heuristic tools for understanding discrete aspects of the human response to trauma.

Advances in the neurobiologic characterization of PTSD have largely relied on available medical technology. Much of what has been discussed in this chapter has grown out of recent advances in psychophysiologic, hormone, and receptor assay methodology. As technology in areas such as brain scanning becomes increasingly refined, it soon will be possible to more accurately delineate acute and longterm stress-induced changes in central and peripheral nervous system functioning. With a clearer understanding of biologic pathophysiology, it should be possible to develop more specific and effective treatments for the often devastating disorder of PTSD.

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